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Stepping-stones and Mediators of Pandemic Expansion—A Context for Humans as Ecological Super-spreaders

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Abstract

Humans represent ecological super-spreaders in the dissemination and introduction of pathogens. These processes, consistent with the dynamics of the Stockholm paradigm, are exemplified in the origin and globalized distributions of SARS-CoV-2 since initial recognition in central Asia during 2019 and 2020. SARS-like viruses are not widespread in mammals but appear widespread in chiropterans. Bats are isolated ecologically from most other assemblages of mammals in terrestrial systems. Humans may be the stepping-stone hosts for broad global dissemination and wider infection (given the opportunity) among diverse assemblages of mammals in which host and viral capacity are compatible. Human globalization mediated insertion in global ecosystems along primary and secondary pathways initially with localized to regional circulation across continents. Origins and persistence of cycles involving variants and viral transmission among other mammals and the potential for secondary exposure (retrocolonization) of people occurs on multidirectional pathways. Humans were responsible for the initial breakdown in ecological isolation of the virus that facilitated colonization events from chiropterans to other mammals. In the absence of these human drivers, environmental or ecological interfaces (boundary zones among habitats) limiting the distribution of SARS-CoV-2 are unlikely to have been crossed, leaving a diverse assemblage of SARS-like viruses (*Sarbecovirus*) remaining relatively hidden and isolated in southeast Asia.

Keywords: emerging pathogens, SARS-CoV-2, Stockholm paradigm, host colonization, ecological super-spreaders, geographic range expansion

Introduction

Humans may be the ultimate *ecological super-spreaders* in the dissemination and introduction of pathogens (Boeger et al., 2022). In the case of COVID-19, humans are at the nexus of a dynamic stepping-stone that has mediated the distribution of the SARS-CoV-2 virus from focal interfaces (i.e., boundary zones among habitats) of localities and landscapes to eruptive expansion crossing the artificial boundaries that link regional and global scales of urban environments and terrestrial ecosystems in ecological time (Araujo et al., 2015; Morens and Fauci, 2020). Critically, there was limited opportunity for pathogen emergence in the absence of human hosts as facilitators in the disruption of ecological isolation and barriers among a diverse spectrum of potential mammalian host species and across geography. Globalization and waves of human dispersal mediated the introduction, broad establishment, and circulation of the virus among assemblages of human and other mammalian hosts in wildland, agricultural, and urban environments (Rochman et al., 2021; Pekar et al., 2022).

In the highly fluid circumstances of a global pandemic, SARS-CoV-2 had already been documented in 200 countries, with +183 million human cases and nearly 4 million fatalities attributed to COVID-19 as of July 2021 (Lin et al., 2021). Circulation in humans and a broadening diversity of mammalian hosts among the Carnivora (Canidae, Felidae, Mustelidae), Cetartiodactyla, Primates, and Rodentia has been documented across all continents of the northern and southern hemisphere, excluding Antarctica (e.g., Gryseels et al., 2020; Mahdy et al., 2020; Chang, 2021; Jia et al., 2021; Lin et al., 2021; Wei et al., 2021; Hale et al., 2022; Kuchipudi et al., 2022; Martins et al., 2022; Padilla-Blanco et al., 2022; Pickering et al., 2022; Yen et al., 2022). High diversity and extensive distribution provide conditions for a complex mosaic of virus-host interactions and global persistence through single and multiple events for introduction and establishment with recurrent expansion, isolation, and oscillations across geography and host range (Deng et al., 2020; Rochman et al., 2021; Colson et al., 2022).

SARS-2 Variants and Stockholm Paradigm

Pathogen diversity, including the origins of SARS variants, is generated through repeated cycles (oscillations) of expansion and contraction of host and geographic ranges (Brooks et al., 2019; Boeger et al., 2022). Cycles of isolation occur both in people and assemblages of domestic; semi-domestic; and wild, free-ranging mammals; subsequent expansion and dissemination of initially focal variants occur with relaxed isolation, secondary globalization, and increasing connectivity (Rochman et al., 2021). These pathways define the outcomes of taxon-pulse and oscillation within the dynamics of the Stockholm paradigm (SP) at local, regional, and global scales consistent with a growing body of empirical observations and modeling of the pathogen-host interface (Hoberg and Brooks, 2008, 2015; Araujo et al., 2015; Brooks et al., 2019; Feronato et al., 2021). The history of the SARS-2 pandemic is powerfully predicted and documented by the SP dynamics. Events of colonization occur through ecological fitting (EF) in sloppy fitness space (SFS) (Agosta et al., 2010) in the context of broad capacity to access resources in mammalian hosts, in this case the broad representation of the functional ACE2 receptor across this class of vertebrates (e.g., Conceicao et al., 2020; Temmam et al., 2022; Thakur et al., 2022). Continually shifting patterns for environmental interfaces drive opportunity for geographic and host expansion into an assemblage of potential and recognized reservoirs, including people, mediated by human activities in ecological time (Brooks et al., 2019; Ruiz-Aravena et al., 2021).

Consequently, continuing emergence and reemergence of an assemblage of *Betacoronavirus* (including *Sarbecovirus*, which contains SARS-CoV and SARS-CoV-2) and *Alphacoronavirus* among vertebrates would be anticipated (e.g., Boni et al., 2020; Damas et al., 2020; Latinne et al., 2020). There is a potential for widespread circulation among humans and animals within this assemblage of viruses but notably with human hosts as drivers of complex pathways for distribution and divergent trajectories for selection and viral recombination following initial colonization event(s) (Cai and Cai, 2021; Lin et al., 2021; Mallapaty, 2021; Rochman et al., 2021; Wei et al., 2021; Boeger et al., 2022; Pekar et al., 2022). Recurrent host colonization and geographic isolation, in conjunction with viral recombination, are considered central to diversification in SARS-like viruses (e.g., Anthony et al., 2017; Leopardi et al., 2018).

Succinctly, this suggests that the initial foundations for colonization as a precursor for epidemic and pandemic events *can be predicted or anticipated*, based on the interaction of pathogen capacity and environmental opportunity (Brooks et al., 2014; Araujo et al., 2015; Brooks et

al., 2019; Boeger et al., 2022). In contrast, the outcomes of cyclic expansion and isolation in the accumulation of mutations and origins of an array of variants reflecting geography and hosts *cannot be predicted*. Thus, two distinct pathways in pre- and post-pandemic expansion can be recognized (e.g., Wei et al., 2021). Despite genetic recombination and the accumulation of mutations following initial colonization, the evolutionarily conserved mechanism of infection (the interaction of spike proteins and ACE2 receptors) has not been substantially modified, and the potential remains for considerable and continuing involvement of global mammalian diversity (Temmam et al., 2022). Consequently, the basis for prediction is the period preceding initial colonization—signifying the critical importance of DAMA (Document, Assess, Monitor, Act) trajectories in revealing baselines for host and geographic distributions and connectivity for a diversity of pathogens and the identification of the probable interfaces and reservoirs for circulation (Brooks et al., 2014, 2019; Trivellone et al., 2022).

Although the focus has remained on chiropterans and *Coronavirus* (e.g., Latinne et al., 2020; Ruiz-Aravena et al., 2021; Zhou et al., 2021; Holmes, 2022), the recognition of SP dynamics and the pervasive nature of colonization of new hosts (Hoberg and Brooks, 2008; Hoberg, 2010; Brooks et al., 2014, 2019; Boeger et al., 2022) suggests further explorations of diversity should occur at the interfaces of connectivity among assemblages of potential mammalian hosts and reservoirs in sympatry. Invasion biology, a subset within these dynamics, would also contribute to the changing landscape for colonization and emergence through opportunities originating from movement and introduction of novel pathogen-host assemblages (Hoberg, 2010; Laaksonen et al., 2015; Malcicka et al., 2015; Zhang et al., 2022). Targeted, strategic biodiversity inventory encompassing a broad array of mammalian species (e.g., in the context of coronaviruses and other pathogens), and more broadly among domestic and migratory avian species, along with accumulation of archival resources of specimens and information, remain essential (Hoberg, 2010; Hoberg et al., 2013; Brooks et al., 2014; Dunnum et al., 2017; Brooks et al., 2019; Colella et al., 2021). Further, comprehensive sampling across arrays of potential vertebrate and invertebrate host species in interface environments is inadequate and has focused predominantly on synanthropic/domesticated mammals and birds (e.g., Cleaveland et al., 2001), leaving an extensive minefield of hosts and pathogens that have yet to be surveyed strategically (e.g., Brooks and Ferrao, 2005; Brooks et al., 2014, 2019).

Humans, Pathogens, and the Biosphere

Recognizing humans as mediators of expansion and introduction for enzootic pathogens, including many viruses that threaten food security (e.g., African Swine Fever Virus, Rabbit Haemorrhagic Fever Virus, African Cassava Mosaic Virus) and the synanthropic assemblages associated with plague and cholera, is not especially remarkable (e.g., Daszak et al. 2000; Brooks et al., 2019; Ranawaka et al., 2020; Huang et al., 2021; Stephens et al., 2021; Brooks et al., 2022; Fagre et al., 2022; Trivellone et al., 2022). Humans are also facilitators of environmental change and disruption, such as climate warming and anthropogenic forcing (e.g., Barnosky et al., 2012; Pecl et al., 2017), which drive and influence associations for assemblages of zoonotic and other pathogens across wildland and managed ecosystems (e.g., Hoberg, 2010; Brooks and Hoberg, 2013; Kafle et al., 2020; Glidden et al., 2021; Brooks et al., 2022). Under most scenarios of perturbation and emergence, the prevailing impression has remained that novel genetic change in a pathogen is most often the precursor for host colonization, or acquisition of novel hosts, and that such mutations are conveniently waiting in the wings for an opportunity (Parrish et al., 2008; discussed in Agosta et al., 2010; Brooks et al., 2019, Huang et al., 2021). Humans have historically driven epidemic and enzootic emergence and spread, including the 1918 influenza pandemic that originated from an avian source and subsequently swept around the globe (Worobey et al., 2014). Significantly, the generality of a stepping-stone pathway for some influenza outbreaks has also been recognized, with transmission from avian hosts to humans and secondarily to swine (Nelson and Worobey, 2018). People appear to have facilitated the initial expansion of SARS-CoV-2 in conjunction with the cascade and crash of food resources in China emerging from the impact of African Swine Fever (Lytras et al., 2021; Xia et al., 2021; Brooks et al., 2022). The emergence of SARS-CoV-2 is, so far, a singular but not unique event, with human hosts serving concurrently as reservoirs and stepping-stones (geographically and ecologically), leading to widespread introduction and establishment across ecosystems. People are mediators and facilitators on pathways with direct and indirect involvement. These circumstances can establish long-term pathogen pollution (Daszak et al., 2000; Gryseels et al., 2020; Mahdy et al., 2020) and a refuge and potential source for continued cycles of human infection and retrocolonization (Cai and Cai, 2021; Lytras et al., 2021; Mallapaty, 2022).

SARS-CoV-2 has been under intense focus as the initial pandemic during an era of rapid technology for which

resources for expeditious sequencing linked to science infrastructure provide essential tools to track the history of emergence and globalization (e.g., Chen et al., 2022). An increasingly robust toolkit for pathogen exploration may demonstrate generalities about past and future pandemics. Notably, the behavior of Zika and Dengue viruses across environmental and host interfaces, although having greater complexity as arboviruses with arthropod vectors, may parallel the potential for emergence now recognized during the current pandemic (e.g., Brady and Hay, 2020; Regala-Nava et al., 2022). Further, with respect to colonization, stepping-stone dynamics, and persistence under the SP, Zika has oscillated into animals such as water buffaloes, rats, hippopotamus, and many other species, including exploitation of new world monkeys (Vorou, 2016). A multihost, multivector pathway (for Zika) may involve acquisition of alternative arthropod vectors that reflect expansion and movement, with ecological fitting, over extensive geographic space through introduction (Brady and Hay, 2019; Ryan et al., 2021), exemplified by the temperate zone vector, *Aedes albopictus* (Oliveira et al., 2021). The implication for colonization across tropical, subtropical, and temperate biomes and increasingly higher-latitude landscapes under temperature warming and environmental change is notable.

The current focus for viral exploration has remained centered on chiropterans as primary sources of zoonotic pathogens (e.g., Li et al., 2005; Young and Olival, 2016; Latinne et al., 2020; Valitutto et al., 2020; Zhou et al. 2021). Bats are associated with a broad range of viral pathogens, causative agents of realized or potential zoonoses (Dobson, 2005; Olival et al., 2017; Streicker and Gilbert, 2020), but the frequency of focused encounters with people is low, and as a consequence, colonization directly to humans is rare (Holmes et al., 2022). Acquisition of human hosts by such zoonotic pathogens as Ebola virus, Marburg virus, and a diverse array of *Coronavirus* is relatively infrequent, depending on heightened or focused propagule pressure in closed environments and restricted proximity (Feronato et al., 2021; Ruiz-Aravena et al., 2021). *Coronaviruses* are ubiquitous in mammals but are generally restricted in distribution to particular mammalian taxa; there are now 7 known "human" coronaviruses, most with potential zoonotic origins or sources in wild or domestic mammalian hosts (Zhou et al., 2021). Colonization events represent the interface for pathogen capacity, environmental opportunity, and ecological fitting in sloppy fitness space which facilitate host shifts in space and time (Brooks et al., 2019). Colonization requires a stepping-stone linkage from bats to humans, or from bats to other potential mammalian species, that may be synchronic and sympatric; ecological fitting and sloppy fitness space bridge the nexus for capacity and opportunity (Araujo et al., 2015; Morens and Fauci, 2020; Holmes, 2022). General concerns for pandemic expansion extend beyond SARS-like viruses, notably for such zoonotic pathogens as Ebola virus, which could become established in an enzootic cycle from human sources and secondarily from assemblages in other mammals as a source for human infection, following human introduction and dissemination. The arboviruses, such as Dengue, Yellow Fever, and Chikungunya, exhibit high propagule pressure but are temporally limited; although there is the potential for seasonally defined global networks linking the southern and northern hemisphere with widespread translocation/introduction/establishment of arthropod vectors, amplifying hosts and direct movement of infected people (Vorou, 2016). However, the context for introductions and establishment of Zika are further confounded by spread through associations with a broadening array of vectors and the potential sexual transmission among human hosts (e.g., Counotte et al., 2018; Mead et al., 2018; Apari et al., 2019).

Pathogens with complex life cycles involving multiple hosts (including vectors and intermediates) need to be properly considered in multitrophic models to evaluate pathways for colonization and potential rates for dissemination. Pathogens that circulate among an assemblage of hosts and across trophic levels, although existing in considerable SFS, may be temporally buffered with potentially slower rates of geographic colonization or spread, which is pertinent to arboviruses, plant pathogens, and most helminths that circulate through arthropods, other invertebrates, and vertebrates. In this sense, and in contrast to viruses (and SARS-CoV-2, in this case) with direct transmission, "enormous SFS plus special conditions" for complex life cycles may be no more restrictive than "smaller SFS plus less special conditions" for simple life cycles, a generality that can benefit from deeper exploration (e.g., Brooks et al., 2006; Malcicka et al., 2015; Brooks et al., 2019; Agosta and Brooks, 2020).

Colonization requires focused circumstances at ecological interfaces with considerable propagule (exploration) pressure to complete infection pathways to people. Conditions of heightened propagule pressure, with an assemblage of *Sarbecovirus*, have been recognized in bat caves and among guano miners in Southeast Asia (Wacharapluesadee et al., 2013; Joyjinda et al., 2019). Genetically diverse *Sarbecovirus* are most apparent in species-rich assemblages of chiropterans, especially species of rhinolophid bats, from southern China and borderland regions of Myanmar, Thailand, Laos, Cambodia, and Vietnam (e.g., Li et al., 2005; Latinne et al., 2020; Mallapaty, 2021; Zhou et al., 2021; Temmam et al., 2022). A remarkable diversity of bat coronaviruses is isolated at local/landscape scales in this region and

apparently lacks broader interaction with other terrestrial mammals in sympatry in cave habitats (Li et al., 2005; Valitutto et al., 2020; Zhou et al., 2021). Extensive host switching among bats and recombination among viral populations at fine geographic scales are considered among the primary drivers of diversification among the lineages of *Sarbecovirus* including these SARS-like viruses (Huyhn et al., 2012; Werthheim et al., 2013; Corman et al., 2015; Anthony et al., 2017; Leopardi et al., 2018; Latinne et al., 2020). Ecological isolation of chiropteran species in dispersed cave environments could drive partitions in this community that would limit direct human exposures. It has been estimated, however, that nearly 400,000 people in Southeast Asia are infected annually with SARS-related viruses originating in bats, with these infections largely being undetected and undiagnosed (McCarthy, 2021). But in general, casual interfaces appear insufficient in facilitating a concurrent concentration or a focused interface of infective virus and susceptible potential human hosts. Thus, the particular circumstances represented by animal wet markets in Wuhan and other urban centers in China and Southeast Asia are of significance in providing initial stepping-stone pathways for amplification and dissemination of SARS-like and related viruses from bats through live wildlife food resources to humans (e.g., Huong et al., 2020; Lytras et al., 2021; Xia et al., 2021; Pekar et al., 2022; Worobey et al., 2022).

Stepping-stone dynamics (Araujo et al., 2015) provided opportunity for SARS-like viruses to bridge relative ecological isolation (of *Betacoronavirus* and *Sarbecovirus* circulating in chiropterans), leading to colonization of humans and synanthropic environments based on preexisting capacities to use widespread resources in mammals. This has occurred minimally on 2 occasions involving betacoronaviruses and food chains for people with SARS-CoV in 2003 and most recently for SARS-CoV-2 in 2019 (Pekar et al., 2022; Worobey et al., 2022), and possibly represented with emergence of MERS-CoV (Ruiz-Aravena et al., 2021; Zhou and Shi, 2021; Zhou et al., 2021). Closely related SARS-like coronaviruses are not common outside of bats in other mammalian groups in sympatry, although diversity of enteric and respiratory coronaviruses is well documented (e.g., Lin et al., 2021). With respect to SARS and SARS-2, these viruses would likely have remained limited in distribution by ecological isolation (and it appears diversifying in Southeast Asia—see Latinne et al., 2020; Holmes, 2022) in the absence of human activities.

Observations related to colonization indicate a fundamentally important interaction for capacity and opportunity. As we have noted, although capacity is apparent for SARS-like viruses to utilize widespread host resources and thus a broad range of mammalian hosts, opportunity had been strongly limited by ecological context. In contrast, the fluid structure of interfaces, within common environmental settings and with ecological connectivity, has been demonstrated for a diverse assemblage of viruses, showing frequent patterns of colonization among giant panda (*Ailuropoda melanoleuca*) and associated mammalian hosts (Zhao et al., 2022). Interfaces and colonization thus reflect the degree of sympatry or synchrony relative to real exposures and focused propagule pressure across potential host assemblages in shared environments (Guerrero-Sanchez et al., 2022).

Significantly, the origin of the Omicron variant of SARS-CoV-2 was suggested to be associated with rodent hosts, with a source of original infection constituting an initial stepping-stone pathway facilitated by a human reservoir host in Africa during 2020 (Wei et al., 2021). The Omicron variant remained in relative isolation and on a divergent selection trajectory for a period of time preceding subsequent retrocolonization of humans and rapid geographic expansion globally (Sun et al., 2021; Wei et al., 2021; Boeger et al., 2022). The implications of ubiquitous rodent hosts for SARS-like viruses are considerable. The history for highly divergent variants, with emergence and expansion of SARS-2 among populations of white-tailed deer (in a stepping-stone dynamic of humans—semidomesticated captive deer on game farms—deer in wildland habitats and retrocolonization to humans), is another exemplar of recurrent opportunity meeting capacity mediated by human behaviors that facilitate focused propagule pressure necessary to drive colonization (Hale et al., 2022; Kuchipudi et al., 2022; Mallapaty, 2022; Pickering et al., 2022; Roundy et al., 2022). Thus, the overall pathways for the pandemic are apparent, from its focal origins to the present juncture, with independent episodes of expansion, isolation, and diversification of viral variants among free-ranging wildlife, synanthropic mammalian hosts, and humans (**Figure 1**). Such cascading events for pathogen dissemination among people and across ecosystems are a component of the larger pervasive impact of humans in the biosphere.

Humans as Ecological Super-spreaders

Human activity and behavior (mobility, connectivity, interfaces) leads to breakdown in ecological isolation from and among other species, providing opportunity for host colonization. In the absence of human reservoirs, stepping-stones, and mediators, the complex of SARS-like viruses would likely remain isolated. Human interactions changed the dynamic among these viruses from *exploitation mode* in isolation—where they use their inherited capacities to exploit the conditions (e.g., host-based resources and hosts)

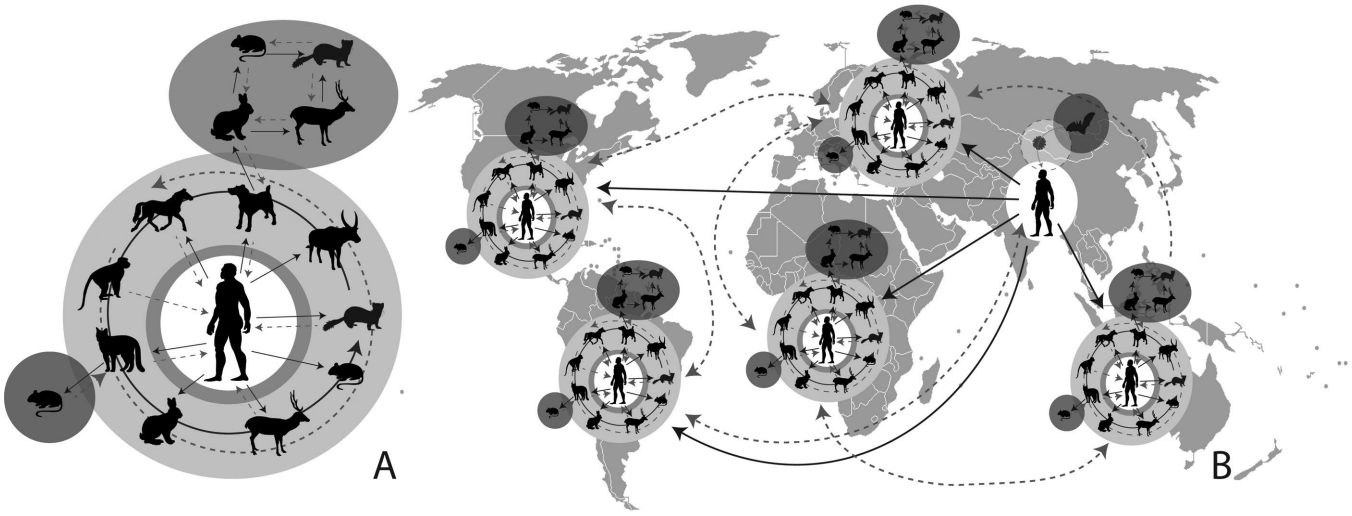

Figure 1. The complex dynamics of a pandemic compatible with the Stockholm paradigm as revealed by COVID-19. **A.** A diagrammatic representation of circulation of a pathogen with humans as ecological super-spreaders, involving transmission among realms of urban, periurban, and wildlife species (circles and ovate spaces). Overlapping of each realm (darker gray) represents the zone of interface, where pathogen exchanges may occur between realms—a process which may vary spatially, temporally, and at local scales because of inherent characteristics of the mammalian assemblages (e.g., diversity, behavior of periurban species, environmental characteristics) and humans (e.g., culture, traditions, economics). **B.** Emergence of SARS-CoV-2 in Asia was likely associated with stepping-stone dynamics apparently involving a species of mammal (yet to be definitively identified) that bridged the ecological distance, providing the opportunity between the donor (bats) and the recipient species (humans). Initial stages of the pandemic were driven by human movements around the planet, spreading the virus across regions and continents (solid arrows). Connectivity mediated by humans disseminated or inserted SARS-CoV-2 into new systems of exploration, initially into urban and periurban realms and subsequently forming a complex network of transmission and emergence also involving the wildlife realm. Emergence across new realms, with distinct geographic and environmental contexts, resulted from multiple trajectories (events) of expansion and exploration over time, with subsequent potential for isolation and exploitation spatially and temporally, processes that have been demonstrated empirically. These dynamics are postulated in origins of novel variants (under different regimes of selection and isolation) of the pathogen. Given opportunity, such variants (including Delta, Omicron, and others) became disseminated among susceptible mammals, secondarily driving patterns of retrocolonization in humans. Continued expansions linked to globalized travel by humans (dashed arrows) during the course of the pandemic have resulted in subsequent spread of each successive new variant and are the basis for continued cycles of oscillation.

as best they can—to *exploration mode* in expansion—where they use their inherited capacities to cope with changing conditions as best they can by exploring opportunities for EF in SFS, including colonizing new geographic areas and hosts (Brooks et al., 2019; Agosta and Brooks, 2020). *Taxon pulse cycles* (sensu Erwin, 1981) of isolation and expansion along with *oscillations in host range* (sensu Janz and Nylin, 2008) and geographic distribution under the SP, continue to drive perpetuation of the pandemic and broadening exposures on ecosystem scales (e.g., most recently among North American white-tailed deer and people).

In managing a pandemic, exploitation mode in isolation is synonymous with "lockdown mode," creating the ideal conditions for the accumulation of mutations and emergence of novel variants (Brooks et al., 2019; Agosta and Brooks, 2020). The "opening mode" after lockdown is synonymous with exploration mode during expansion, creating the ideal conditions for novel variants to expand their geographic and host ranges. The cycle of lockdown and open links fine-scale population dynamics and genetic structure to global distributions of pathogens, serving to demonstrate the signatures of taxon pulse and oscillation in shallow ecological time (Rochman et al., 2021; Boeger et al., 2022). New pathogen diversity is generated in isolation, and propagule pressure at ecological interfaces fuels the exploration of new hosts during geographic expansion (Feronato et al., 2021). Thus, events unfolding at local and landscape levels in conjunction with human behavior and incomplete biodiversity knowledge have global consequences. We should be exploring these interfaces through

targeted field-based sampling of potential and recognized host assemblages to reveal the signatures of genetic diversity and demographics associated with pathogen circulation (e.g., Brooks et al., 2014; Colella et al., 2021; Padilla-Blanco et al., 2022; Trivellone et al., 2022). The distribution of genetic diversity reveals viral origins, geographically independent events of host colonization, and multifaceted pathways for transmission during the course of the pandemic involving a considerable component of the global mammalian fauna (e.g., Oude Munnink et al., 2020; Cai and Cai, 2021; Rochman et al., 2021; Wei et al., 2021; Boeger et al., 2022; Pickering et al., 2022).

Humans represent a new epidemiological class that can be considered as *ecological super-spreaders* in the dissemination and introduction of pathogens (**Figure 1**) (Boeger et al., 2022), contrasting with the recognition of super-spreader events associated with human-human transmission (e.g., Koelle et al., 2022). SARS-like viruses are not widespread in mammals but appear widespread in bats. Bats are isolated ecologically from most other assemblages of mammals in terrestrial systems. COVID-19 is just one example of how humans may be the stepping-stone hosts for broad global dissemination and wider infection (opportunity) among diverse assemblages of mammals in which host and viral capacity are concordant (Kuchipudi et al., 2022). Human globalization mediated insertion of SARS-CoV-2 in global ecosystems, with origins and persistence of cycles of viral transmission among other mammals and the potential for secondary exposure (retrocolonization) of people in multidirectional pathways (Oude Munnink et al., 2020; Cai and Cai, 2021; Lytras et al., 2021; Wei et al., 2021; Boeger et al., 2022; Mallapaty, 2022; Pickering et al., 2022). Although such events across a broad spectrum of potential pathogens involving colonization from humans and retrocolonization from wild and synanthropic hosts appear infrequently, such ecologically mediated colonization, as with SARS-CoV-2 is consequential (Fagre et al., 2022). Emphasized is the nexus for opportunity/capacity and fitness space, which effectively changes the narrative (from adaptation and special mutation), indicating the subtle tipping points in distribution that can drive pandemic expansion across hosts, geography, and time (Audy, 1958; Brooks et al., 2019). Further, by providing an opportunity for colonization of new hosts in different communities and across geography, we (humans) may further maximize the emergence of new variants with circulation (oscillation) of the virus in wildlife networks at landscape scales with subsequent expansion globally. Connectivity through environmental interfaces within this network, linking urban, periurban, agroscapes, and wildland habitats could create multiple pathways for retrocolonization back to humans (Colson et al., 2022).

The term "spillover" has been proposed as a general description for these events (Daszak et al., 2000), but it is not appropriate because rather than residing on the periphery of pathogen circulation, people are active reservoirs of infection. Humans are at the center of dynamic (multidirectional) expansion and diversification on ecosystem scales involving an increasing number of independent events for host and geographic colonization (**Figure 1**). Spillover and "spillback" are anachronistic terms that describe the dynamics of emergent pathogens. Both are tied conceptually to a considerable legacy of a standard model for "maximum coevolution and cospeciation" of parasite-host relationships that has codified often misleading assumptions about pathogen distribution and evolution (e.g., Hoberg and Brooks, 2008; Agosta et al., 2010; Brooks et al., 2015): spillover (and spillback) (1) assumes a primary or single host (one host–one pathogen) in which the pathogen is limited in distribution and circulation through a history of cospeciation and increasing specialization; (2) perpetuates the concept of emerging infectious disease (EID) as rare or unpredictable events because the potential is limited by cospeciation between pathogen and host; and (3) perpetuates the idea of EID requiring special adaptation, i.e., that variants represent specific adaptations that drive ongoing expansion events.

Spillover is simply another term for the broader concept of biotic expansion, which applies to changing patterns of host and geographic range. The SP provides a realistic picture of complexity in the biosphere with the potential and propensity for colonization events linking pathogens, hosts, time, and geography as drivers of continual episodes of EID. Clearly, "one host–one pathogen" has limited explanatory power when describing the dynamics of pathogen emergence and spread. Further, the taxon pulse, a central dynamic of this pandemic, is a component of the Stockholm paradigm synthesis and the geographic form of the oscillation hypothesis. Thus, biotic expansions, common in Earth history, open up geographic fitness space, creating opportunities for host range expansion (Hoberg and Brooks, 2008; Brooks et al., 2019; Agosta and Brooks, 2020).

The history surrounding the emergence of the Omicron variants and the larger progression of the pandemic are consistent with SP dynamics, pre- and post-colonization (Boeger et al., 2022). Pre-colonization, the ability to have predicted this initial outbreak was substantial from the perspective of the SP, consistent with the evolutionarily conserved nature of the ACE2 pathway for infection, creating a link between pathogen capacity and ecological conditions (opportunity) for colonization. Post-colonization dynamics, however, cannot be predicted, reflecting the outcomes of recurrent taxon pulse cycles and oscillations in host range

(and geography), producing a growing array of variants and their downstream circulation to new hosts. This recombination and accumulation of mutations over global geographic space greatly increases the unpredictability and complexity of the problem. What does not change, however, is the conservative mechanism for infection (i.e., spike proteins and ACE2 receptors), ensuring that the capacity for host switching by EF in SFS among the entire assemblage of mammals is extensive and, as we have observed, is likely, if given the opportunity. The essential point is that the basis for prediction and prevention of EID is *before* the colonization event. This brings into focus the critical importance of protocols like DAMA, aimed at defining the distribution and connections for diversity of pathogens and their hosts with the identification of the probable interfaces (Brooks et al., 2019; Boeger et al., 2022; Brooks et al., 2022; Trivellone et al., 2022). SARS-CoV-2 and the proliferation of its variants is a powerful exemplar for the universality of pathogen circulation and EID, providing strong proof of concept and validation for the SP as a general framework for understanding their dynamics.

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